Current Hypertension Reports (2018) 20: 74
https://doi.org/10.1007/s11906-018-0874-y

SLEEP AND HYPERTENSION (SJ THOMAS, SECTION EDITOR)

Sympathetic Nervous System, Sleep, and Hypertension

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Published online: 6 July 2018

Abstract
Purpose of Review To evaluate the relation between sleep alterations, with or without breathing disorders, and incidence of hypertension and other cardiovascular diseases
Recent Findings Several studies have clearly shown the mechanisms linking sleep disorders and cardiovascular diseases. The sympathetic hyperactivity seems to play a fundamental role in favoring and sustaining the increase in blood pressure values. Several other mechanisms also contribute to this effect and to the increase cardiovascular risk.
Summary The mechanisms responsible for the increase in blood pressure values in subjects with alteration in sleep quantity and quality, with or without breathing disorders, have been clearly established. The recent findings refer to the result of meta-analysis of cross-sectional studies or longitudinal studies showing a significant association between short sleep duration and hypertension. It has also been shown that sleep fragmentation could be considered the main determinant of the sympathetic activation independently of the frequency and severity of oxygen desaturation.

Keywords Hypertension · Sympathetic nervous system · Sleep apnea · Sleep disorders · Cardiovascular risk · Autonomic control

Introduction

Hypertension is a major public health epidemic with a prevalence that has been estimated to affect more than 3.5 billion people in 2015 (those with systolic blood pressure over 110 to 115). It represents a risk factor for ischemic heart disease, stroke, and cardiac and renal failure [1, 2]. The relation between the increase in blood pressure (BP) values and the activation of sympathetic nervous system due to the concomitant stimulation of several mechanisms have been clearly established [3]. It has been also shown that a hyperadrenergic tone is just present in high-normal blood pressure indicating that sympathetic activation may precede overt arterial hypertension even in very low-risk subjects [4]. Disorders of sleep may greatly influence blood pressure levels contributing to the increase cardiovascular morbidity and mortality irrespective of the 24-h BP levels [5]. In this review, we will see the role of sleep in modulating BP values and the impact of sleep disorders and pathophysiological conditions on sympathetic tone and BP.

This article is part of the Topical Collection on *Sleep and Hypertension*

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Sleep: Phases and Mechanisms

Normally, sleep consists of cycles with alternation between non-rapid eye movement (NREM) and rapid eye movement (REM). These phases are characterized by important physiological changes in respiratory and cardiovascular functions. NREM sleep is prominent at the beginning of the night and is accompanied by a progressive decrease of sympathetic nerve activity to the vasculature and a progressive increase in parasympathetic cardiac modulation leading to a reduction in blood pressure and heart rate variability and an increase in arterial baroreflex sensitivity [6, 7]. This phase is also characterized by changes in breathing patterns with a shift to automatic mechanisms. This induces a slower and more regular respiration and contributes itself to changes in the nocturnal modulation of BP and heart rate [8]. REM sleep and awake are characterized by a significant and highly variable increase in sympathetic activity and BP levels. Baroreflex sensitivity increases during sleep but is more effective in buffering increases in BP during REM episodes in the last part of the sleep. Alterations in these physiological mechanisms may

contribute to the hemodynamic and neuroadrenergic alterations favoring and sustaining hypertension.

Blood Pressure During the Night

During the night, healthy individuals did not show significant changes in cardiac output and the reduction in BP values is due to a decrease in sympathetic output and in total peripheral vascular resistance. Usually, a decrease of 10 to 20% in mean systolic and diastolic nocturnal BP compared with mean daytime values is considered normal. An absence of nocturnal dipping or a decrease in mean systolic and diastolic BP greater than 20% of mean daytime values (extreme dipping) or an increase in nocturnal BP values compared to mean daytime values (reverse dipping) are conditions characterized by an alteration in a fundamental mechanism participating in day and night cardiovascular modulation such as the adrenergic nervous system [9]. The reverse dipping state, observed in a group of essential hypertensives, is characterized by a sympathetic activation greater for magnitude than that seen in the other conditions displaying abnormalities in nighttime BP pattern [10]. As regards the possible mechanisms, these appear not to be due to baroreflex function but to metabolic ones, i.e., insulin resistance, thus reflecting the multifold circulatory effects of insulin (vasomotor response, central action, alteration in neural sympathetic drive) [11].

Several studies have also shown that the reduction in dipping pattern represents a strong and independent predictor of cardiovascular risk [12, 13]. The Dublin Outcome Study and other studies have also shown that nocturnal BP is a better predictor of cardiovascular risk than daytime BP [14–16].

Sleep Disorders

Sleep is essential for optimal health. An increase number of studies and epidemiological data have shown a relation between insufficient rest or poor quality of sleep and hypertension and outcomes [17, 18, 19••, 20••]. We will consider the effects of the three main conditions associated with sleep alteration: sleep deprivation, changes in sleep duration and quality, and insomnia.

Sleep Deprivation

Several studies have shown that short-term sleep deprivation is associated with an increase in systolic and diastolic BP and heart rate during the day after. This is also accompanied by an increase in urinary excretion of norepinephrine [21]. This was the case also for moderate sleep deprivation which was accompanied by changes in heart rate and BP variability [22]. The sympathetic activation and the decrease in parasympathetic modulation appears to be the result of a reduction of NREM-sleep compared to REM-sleep. Studies of total sleep deprivation have shown a BP increase accompanied by a reduction in adrenergic tone due to a resetting of the sympathetic arterial baroreflex [23].

Sleep Duration and/or Quality

In the last decades, a decrease in sleep duration by 1.5 to 2.0 h/day has been observed in two American community-based cohort studies [24, 25]. These studies have shown that a sleep duration lower than 6 h/night is associated with higher BP values and with a higher risk of incident hypertension in the 10-year follow-up period. In particular, this association is evident in middle-aged subjects (less than 60 years old) [26, 27]. Although most of these studies used self-reported sleep duration; nevertheless, it has been shown that data obtained by questionnaires are valid when compared with data obtained by actimetry [28]. A recent systematic review and meta-analysis [19••] reported a significant association between both short and long sleep duration and prevalent hypertension or between short sleep duration and incident hypertension. This evidence was found only among women and not in European population, but explanation remains uncertain.

The quality of sleep is also of primary importance due to the association with several pathophysiological conditions [29, 30•, 31] and to the association with accidents, quality of life, fatigue, anxiety, physical complaints, and diurnal-reduced cognitive performance [32••]. Prevalence rates of poor sleep quality range between 10 and 48% depending on the criteria and measurement techniques used. The Pittsburg Sleep Quality Index (PSQI) is the most often used self-report instrument for assessing sleep quality [33•]. In a study on about 19,000 individuals from five European countries, it has been shown that restless legs syndrome, characterized by dysesthesia and leg restlessness at night during periods of immobility, was present in the 3.85%, and these subjects presented a twofold higher risk for elevated BP [34]. These data have been confirmed in a systematic review addressing the link between restless legs syndrome and hypertension [35]. These subjects show also a high prevalence of left ventricular hypertrophy which reflects the presence of hyperadrenergic conditions [36•].

Insomnia

Insomnia is defined as the difficulty in initiating or maintaining sleep or non-restorative sleep accompanied by daytime consequences of, for example, memory impairment, mood disturbance, and daytime sleepiness. Short-term insomnia is defined by all of the above with a duration < 3 months. For chronic insomnia, the time duration is 3 months [37]. Since sleep has important homeostatic functions, including suppressive effects on the stress system [38] and on the inflammatory

system [39], both sleep loss and insomnia are seen as pathophysiological mechanisms in the activation of the sympathetic nervous system and of pro-inflammatory pathways. This condition is characterized by an activation of the hypothalamic-adrenal axis and the sympathetic nervous system predisposing to the hypertensive state [40]. Normotensive subjects with chronic insomnia have higher nighttime systolic BP and blunted day-to-night systolic BP dipping compared to good sleepers. Insomnia is associated with a significant higher risk (5.1-fold) for hypertension when sleep duration is below 5 h/night [41]. Recent theories suggest the role of high level of cardiovascular arousal as focus for maintenance of insomnia. This is associated with a hyperadrenergic state, an activation of the inflammatory process, an endothelial dysfunction, conditions favoring plaque activation, and cardiovascular events [42, 43]. Systematic reviews and meta-analysis of cross-sectional and longitudinal studies have shown the association between short sleep duration or sleep loss and hypertension [19••, 20••] (Fig. 1).

Breathing Disorders and OSA

Arousal

The use of polysomnographic recording allows to observe the relations between breathing disorders and changes in sleep and hemodynamic parameters. Repetitive arousal for 1 h does not produce overt changes in heart rate or blood pressure values but a change in the autonomic control favoring a gradual accumulation of the effects of sympathetic activation following each arousal, thus offsetting the tendency for sympathetic withdrawal that accompanies natural sleep onset [44]. It has been recently confirmed that sleep fragmentation contribute to sympathetic activation [45••]. This study has shown that the strongest correlation has been observed between sympathetic activity and sleep arousal index, independently by apneic episodes or severity of oxygen desaturation (Table 1). It appears that sleep fragmentation and arousals not only contribute to poor sleep quality but also to adrenergic hyperactivity and cardiovascular morbidity.

Table 1 Correlations between predictive variables and day-time sympathetic discharge

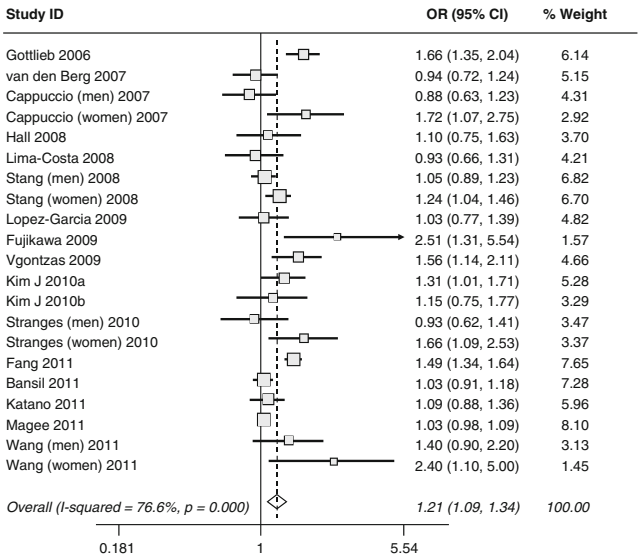
Variables	MSNA (bursts/100 hb)	
Arousal index (events/h)	$r = 0.53$	$p < 0.001$
AHI (events/h)	$r = 0.40$	$p = 0.004$
Age (years)	$r = 0.35$	$p = 0.013$
BMI (kg/m^2)	$r = 0.32$	$p = 0.022$
ODI (events/h)	$r = 0.27$	$p = 0.056$

AHI apnea-hypopnea index, *BMI* body mass index, *ODI* oxygen desaturation index, *MSNA* muscle sympathetic nerve activity, *hb* heart beats

Modified from ref 44

Sleep Apnea

Repetitive collapse of the upper airway and intermittent hypoxia and hypercapnia in the gas exchange induce a sleep disruption, a catecholamine excess, an acute blood pressure increase, a release of inflammatory mediators, and a worsened



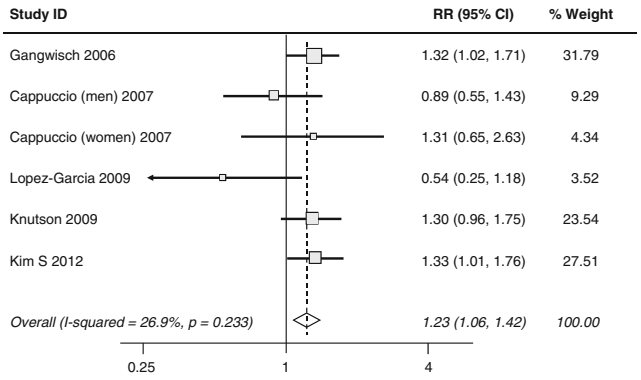


Fig. 1 Left panel shows forest plot of the association between short sleep duration and hypertension from cross sectional studies among adults. Results are expressed as odds ratio (OR) and 95% confidence intervals (95%CI). Right panel shows forest plot of the association between short sleep duration and hypertension from longitudinal studies among adults. Results are expressed as relative risk (RR) and 95% confidence intervals (95%CI). Modified from ref 19

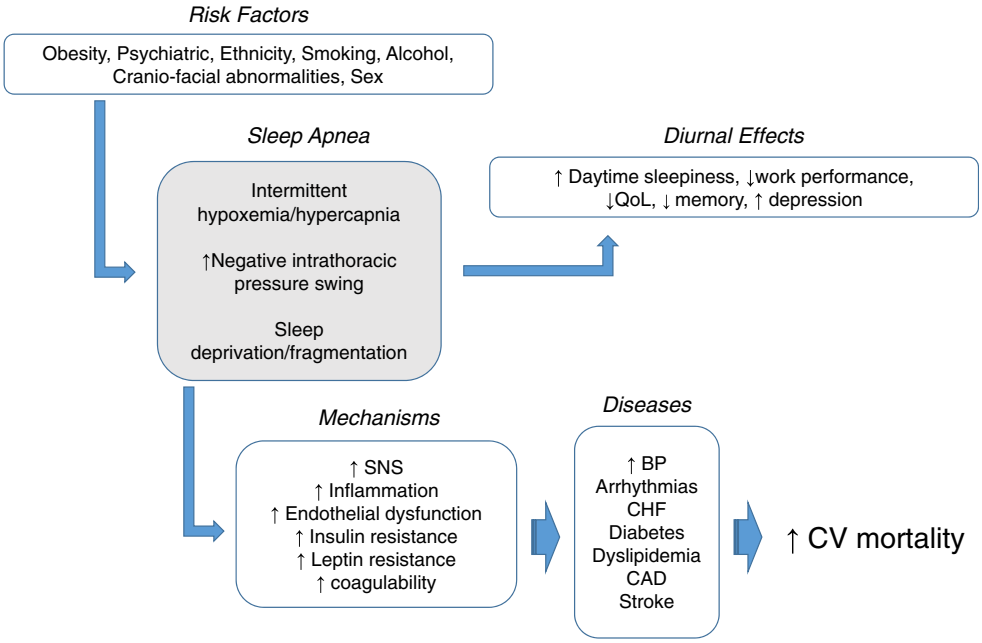


Fig. 2 Mechanisms and consequences of sleep apnea. SNS sympathetic nervous system, CHF congestive heart failure, CAD coronary heart disease, BP blood pressure, CV cardiovascular, Qol quality of life

insulin resistance (Fig. 2). These alterations associated to intrathoracic pressure swing are able to affect preload and afterload and left atrial and ventricular transmural pressure, thus inducing a cardiac remodeling that is frequently present in subjects with sleep apnea (SA) both obstructive (O) or central (C) [46••]. The evaluation of severity is obtained through the assessment of the apnea-hypopnea index (AHI), defined as the average number of apneas and hypopneas per sleep hour. OSA syndrome is based on the presence of increased AHI, excessive daytime sleepiness, oxygen desaturation index, and arousal index [47]. Several studies have clearly shown that OSA appears to be a multifactorial process involving different mechanisms: sympathetic activation, activation of inflammatory pathways, endothelial dysfunction, metabolic dysregulation, and impairment in reflex cardiovascular control [46••, 48–50, 51•, 52•]. Epidemiological research indicates that obstructive sleep apnea is associated with an increased risk of incident hypertension [53] and an incidence and progression of coronary heart disease, heart failure, stroke, and atrial fibrillation [52•, 54••]. The Wisconsin Sleep Cohort Study [53] has shown that subjects with moderate-severe OSA had a 3.2-fold increased odds of developing hypertension; nevertheless, this evidence is not the rule, and in a different cohort, this increased risk was not observed [55]. If OSA contributes to the incidence and progression of hypertension, it is possible to hypothesize that the treatment with continuous positive airway pressure (CPAP) could be able to reduce blood pressure. Reports are conflicting and four meta-analyses [56–59] indicate a modest antihypertensive effect of CPAP. This could be related to the different cohorts, study design, accuracy of BP assessment, degree of CPAP adherence, and to the limited duration of this treatment which is not able to reverse quickly or completely the mechanisms of OSA-induced hypertension. Usually, these patients are also affected by comorbidities that need to be corrected concomitantly to reduce their high cardiovascular risk [60•].

Conclusions

There is a strong evidence for the association of sleep disturbances and sleep-disordered breathing with important impairment in quality of life, and through activation of several mechanisms, with systemic hypertension, glucose intolerance, obesity, coronary artery disease, arrhythmias, and heart failure. Although there is a strong therapeutic rationale for the treatment of sleep apnea, the study that this improves cardiovascular outcome is not secure. Nevertheless, the integration between sleep medicine and cardiology may be very important in increasing behavioral, pharmacological, and device-based interventions for treating sleep disorders and effective in controlling cardiovascular diseases and reducing cardiovascular risk.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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